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09/780,612	02/12/2001	Janardan Kumar	1579-434	9116

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/780,612	KUMAR ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- *The MAILING DATE of this communication appears on the c v r she t with the correspond nce addr ss* --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1 136(a) In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U S C § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1 704(b)

Status

1)☒ Responsive to communication(s) filed on *17 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *9-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8/6/01
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-12 are pending.

2. Applicant's election with traverse of Group I, claims 1-8 drawn to a method of treating a mammal having a disease of the eye characterized by elevated intraocular pressure with the peptide comprising RGD or derivative thereof filed on 7/17/03, is acknowledged.

Applicant's traversal is on the grounds that no udue burden would be placed on the Examiner from the standpoint of searching Groups I and II were rejoined as the two Groups are classed and subclassed identically.

Upon reconsideration Examiner rejoined Group I and Group II (claims 1-8) drawn to a method of treating a mammal having a disease of the eye characterized by elevated intraocular pressure with the peptide comprising RGD or derivative thereof or RGD mimetic thereof.

Otherwise, the requirement is still deemed proper and is therefore made FINAL.

3. Claims 9-12 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-8 are under examination as they read on a method of treating a mammal having a disease of the eye characterized by elevated intraocular pressure with the peptide comprising RGD or derivative thereof or RGD mimetic thereof.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating glaucoma in a mammal comprising administering the peptide GRGDTP (SEQ ID NO:1), does not reasonably provide **enablement** for a method of treating a mammal having any **disease of the eye** characterized by elevated intraocular pressure comprising administering to the eye of said mammal an amount of any **compound** that inhibits the interaction between integrin receptor and extracellular matrix sufficient to effect said treatment in claim 1, any compound comprises **peptide RGD** or **derivative** thereof or **mimetic** thereof in claim 3, a derivative which is any **protease-resistant derivative** in claim 4, a derivative comprises the D-form of the peptide RGD in claim 5, any compound comprises the peptide GRGDTP (SEQ ID NO:1) or **mimetic** thereof or **derivative** thereof in claim 6. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Applicant has not provided sufficient biochemical information that distinctly identifies such "compounds", "RGD" peptides, "derivatives" or "mimetics" thereof other than GRGDTP of SEQ ID NO:1. While any RGD peptide may have some notion of the activity of the "modulating agent", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such agents, commensurate in scope with the claimed invention. The specification fails to provide any guidance on how to make any RGD peptide that can be used to inhibit the interaction between integrin receptor and extracellular matrix.

While the Examiner acknowledges that the RGD containing peptides were well known in the art at the time of the invention, and RGD peptides are bound by surface integrin receptors expressed on endothelial cells. However, the specialized medical literature contains hundreds of reports indicating many RGD-related peptides with different activities and different efficacy.

Applicant is relying upon certain biological activities and the disclosure of a single species to support an entire genus. It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, structurally unrelated amino acids comprising RGD motif-comprising peptide encompassed by the claimed invention other than "SEQ ID NO: 1" would be expected to have greater differences in their activities. Since the amino acid sequence of a polypeptide determines its structure and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification) and detailed knowledge of the ways in which a polypeptide's structure relates to it's functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence comprising RGD motif and in turn utilizing predicted structural determinations to ascertain binding of RGD motifs to the integrins, and finally, what changes can be tolerated with respect thereto is complex and well outside the realm of routing experimentation. Furthermore, the specification discloses the RGE peptide is used as a control peptide for RGD peptide. Thus a single amino acid modification affects the RGD binding to the integrin receptors. Therefore, residues that are directly involved in protein functions such as binding will certainly be among the most conserved.

The claims as written encompass a broad genus of peptides with an unlimited number of possibilities with regard to the length of the polypeptide sequence. One of ordinary skill in the art cannot envision all of the amino encompassed by the breadth of the claims still having same recognition by integrins. Therefore, absent the ability to predict which of these molecules would function as claimed, and given the lack of data on changes critical for activity, for one of skill in

the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

In support, Kogan et al. ((J. Biol. Chem.,1995) disclose that single amino acid can determine the ligand specificity of a selectin and the unpredictable nature of amino acid alterations in adhesion/binding activity (see entire document, including the Discussion). On the basis of the disclosed SEQ ID NO: 1 alone, applicant concludes that the scope of the peptides defined by derivative and mimetic thereof encompassed by the claimed invention can have biological activity to inhibit the interaction between integrin receptor and extracellular matrix and be provided as compound to subjects including human to effectively treat any eye disease including glaucoma. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 1924 (CCPA 1970). Without such guidance, targeting RGD peptides to inhibit the interaction of integrin receptor to the extracellular matrix would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

7. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method of treating glaucoma in a mammal comprising administering the peptide GRGDTP (SEQ ID NO:1).

Applicant is not in possession of a method of treating a mammal having any disease of the eye characterized by elevated intraocular pressure comprising administering to the eye of said mammal an amount of any compound that inhibits the interaction between integrin receptor and extracellular matrix sufficient to effect said treatment in claim 1, wherein said compound comprises any peptide RGD or derivative thereof or mimetic thereof in claim 3, wherein said derivative is any protease-resistant derivative in claim 4, wherein said derivative comprises the D-form of the peptide RGD in claim 5, wherein the compound comprises the peptide GRGDTP (SEQ ID NO:1) or mimetic thereof or derivative thereof in claim 6.

Applicant has disclosed only amino acid of SEQ ID NO: 1 for the treatment of glaucoma; therefore, the skilled artisan cannot envision all the contemplated RGD peptides, derivative thereof, mimetics thereof possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention.

See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-8 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 97/06791 (1997), as is evidenced by Pardrige (Peptide Drug Delivery to the Brain, p247, 1991).

The '791 publication teaches a method for inhibiting angiogenesis (see published claim 1, page 105, in particular) in patient having an eye disease such as neovascular glaucoma (see published claim 10, page 105 in particular) comprising administering a polypeptide selected from the group consisting of cyclo (**Arg-Gly-Asp**-D-Phe-Val) published SEQ ID NO:4, cyclo (Gly-D-**Arg-Gly-Asp**-phe-Val) published SEQ ID NO:6, Cyclo (**Arg-Gly-Asp**-Phe-D-Val) published SEQ ID NO:7, Tyr-Thr-Ala-Glu-Cys-Lys-Pro-Gln-Val-Thr-**Arg-Gly-Asp**-Val-Phe published SEQ ID NO:8, cyclo(**Arg-Gly-Asp**-D-Phe-Asn-MeVal published SEQ ID NO:9 and peptide mimetic such as organic mimetics (see published claims 5 and 21, pages 105-106 in particular). These compounds are considered RGD containing peptides, derivatives and mimetics thereof. The '791 publication further teaches the topical application of RGD containing peptides (pages 63-64, specifically, page 64, lines 19-24) and the administration by injection (see page 27, lines 2-4,

in particular). The '791 publication teaches the treatment of the same glaucoma patient populations with the same compositions to achieve the same therapeutic effect.

Claims 4-5 are included because the '791 publication teaches the use of D-form (e.g. D-Arg in SEQ IDNO:6, D-Phe in SEQ ID NO: above) and cyclo-form (e.g. SEQ ID NO: 4, 6, 7 and 9, supra) of the RGD peptide, which are considered to be a protease-resistant derivative of RGD peptide. Further, as is evidenced by Pardrige that the D-derivatives of the peptides are resistant to aminopeptidease (see page 247, lines 16-18 in particular).

While the '791 publication teaches a method of inhibiting angiogenesis in patient having neovascular glaucoma, it is clear that both the '791 publication and the instant claims administer the same composition comprising the same RGD containing peptide to the same patient to achieve the same results. Thus, "treating glaucoma" is inherent property of the referenced method.

The reference teachings anticipate the claimed invention.

10. Claims 1-3, 6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Avila et al (Ophthalmic Surgery and laser 29(4):309-317 (1998), IDS Ref No. A.

Avila et al teach the use of RGD peptides such as RGD (P602), GRGDSP (p603), GRGDSPCA (p604) and GGRGDSPCA (p605) on Glaucoma Filtration surgery in rabbits by subconjunctival injections of the peptides (see abstract page 309, in particular). Avila et al concluded that such peptides were effective in controlling scar formation in glaucoma filtering surgery (a basic surgical procedure for the treatment of glaucoma). In addition, Avila et al teach that RGD containing sequences are recognized by various integrins and RGD is involved in the adherence between cells and the extracellular matrix (see introduction on pages 309-310).

The reference teachings anticipate the claimed invention.

11. Claims 1-4, 6 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by JP 10017488 A, IDS Ref No. 4, as is evidenced by U.S. Patent No. 5,811,515.

The '488 publication teaches a method of preventing effect for glaucoma by inhibitory activity to intercellular adhesion e.g. human conjunctiva fibroblast and human retinoblastoma comprising administering RGD peptide especially cyclic RGD (see abstract in particular). The '488 publication further teaches that the cyclic peptide comprises an amino acid sequence of cyclic [-**Gly-Arg-Gly**-Asp-Ser-Pro-Ala-].

Claim 4 is included because the '488 publication teaches the use of cyclo-form of the RGD peptide is considered to be resistant to the activity of endogenous proteases and peptidases. Further as is evidenced by the '515 patent that the introduction of a cyclic moiety into a peptide

can result in the peptide having a diminished sensitivity to cellular peptidases (col. 1, lines 36-40 in particular).

The reference teachings anticipate the claimed invention.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/06791 in view of U.S Patent No. 5,683,867.

The teachings of the `791 publication have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of SEQ IDNO:1 (claim 6).

The `867 patent teaches that the Gly-Arg-Gly-Asp-Thr-Pro (patented SEQ ID NO:1) peptide was chosen for generating blended nucleic acid ligands because the Arg-Gly-Asp (RGD) motif in matrix proteins is recognized and bound specifically by proteins of the integrin superfamily of cell adhesion receptors. Integrins bind to such proteins as fibronectin, laminin and vitronectin, at sites containing the RGD sequence. This binding is inhibited by short RGD-containing peptides which bind integrin proteins with a Kd of approximately 10^{-5} M (see col. 8 lines 29-37 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the RGD containing peptides taught by the `791 publication with Gly-Arg-Gly-Asp-Thr-Pro as taught by the `867 patent in a method of treating glaucoma.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the Arg-Gly-Asp (RGD) motif in matrix proteins is recognized and bound specifically by proteins of the integrin superfamily of cell adhesion receptors. Integrins bind to such proteins as fibronectin, laminin and vitronectin, at sites containing the RGD sequence. This

binding is inhibited by short RGD-containing peptides which bind integrin proteins with a Kd of approximately 10^{-5} M as taught by the '867 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claims 1-3, 6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Avila et al (IDS Ref. No. A) in view of U.S Patent No. 5,683,867.

The teachings of the Avila et al have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of SEQ IDNO:1 (claim 6).

The '867 patent teaches that the Gly-Arg-Gly-Asp-Thr-Pro (patented SEQ ID NO:1) peptide was chosen for generating blended nucleic acid ligands because the Arg-Gly-Asp (RGD) motif in matrix proteins is recognized and bound specifically by proteins of the integrin superfamily of cell adhesion receptors. Integrins bind to such proteins as fibronectin, laminin and vitronectin, at sites containing the RGD sequence. This binding is inhibited by short RGD-containing peptides which bind integrin proteins with a Kd of approximately 10^{-5} M (see col. 8 lines 29-37 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the RGD containing peptides taught by the Avila et al with Gly-Arg-Gly-Asp-Thr-Pro as taught by the '867 patent in a method of treating a disease of the eye.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the Arg-Gly-Asp (RGD) motif in matrix proteins is recognized and bound specifically by proteins of the integrin superfamily of cell adhesion receptors. Integrins bind to such proteins as fibronectin, laminin and vitronectin, at sites containing the RGD sequence. This binding is inhibited by short RGD-containing peptides which bind integrin proteins with a Kd of approximately 10^{-5} M as taught by the '867 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claims 1-4, 6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 100017488 A (IDS Ref. No. 4) in view of U.S Patent No. 5,683,867.

The teachings of the '488 publication have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of SEQ IDNO:1 (claim 6).

The '867 patent teaches that the Gly-Arg-Gly-Asp-Thr-Pro (patented SEQ ID NO:1) peptide was chosen for generating blended nucleic acid ligands because the Arg-Gly-Asp (RGD) motif in matrix proteins is recognized and bound specifically by proteins of the integrin superfamily of cell adhesion receptors. Integrins bind to such proteins as fibronectin, laminin and vitronectin, at sites containing the RGD sequence. This binding is inhibited by short RGD-containing peptides which bind integrin proteins with a Kd of approximately 10^{-5} M (see col. 8 lines 29-37 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the RGD containing peptides taught by the '488 publication with Gly-Arg-Gly-Asp-Thr-Pro as taught by the '867 patent in a method of treating glaucoma.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the Arg-Gly-Asp (RGD) motif in matrix proteins is recognized and bound specifically by proteins of the integrin superfamily of cell adhesion receptors. Integrins bind to such proteins as fibronectin, laminin and vitronectin, at sites containing the RGD sequence. This binding is inhibited by short RGD-containing peptides which bind integrin proteins with a Kd of approximately 10^{-5} M as taught by the '867 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. Claims 1-6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Avila et al (IDS Ref. No. A) in view of U.S Patent No. 5,683,867 and Pardrige (Peptide Drug Delivery to the Brain, p247, 1991).

The teachings of the '867 patent and the Avila et al reference have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of a protease-resistant derivative in claim 4 and the D-form of the peptide RGD in claim 5.

Pardridge teaches a strategy for developing aminopeptidase-resistant analogues by using the D-derivatives of the peptides that are resistant to aminopeptidease (see page 247, 16-18 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to develop the D-form of the RGD peptides taught by the `Avila et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the D-form is aminopeptidase resistant as taught by Pardridge.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5, 629, 294, or WO 97/06791 or Avila et al or JP 10017488 A each in view of U.S Patent No. 5,041,450.

The teachings of the ` 294 patent, the `791 publication, the `488 publication and the Avila et al reference have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of administered topically in claim 7 or by injection in claim 8.

The `450 patent teaches a pharmaceutical composition comprising matrine particularly directed to the treatment of ocular inflammation. The `450 patent teaches that a decided practical advantage is that the active compound may be administered in a convenient manner such as topically, or by intraocular or intraperitoneal injection. (see col. 2, line 66 through col. 3 line 18 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to administer the RGD peptides taught by the ` 294 patent, the `791 publication, the `488 publication and the Avila et al reference topically or by injection as taught by the `450 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so for the convenience taught by the ` 450 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
October 14, 2003

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
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